THE REMARKS

Claims 2-25 are pending in the application. Claims 2 and 16-21 are withdrawn in view of the Restriction Requirement.

35 U.S.C. §103(a) Rejections

Claims 3-15 and 22-25 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over the combination of Zamecnik, US 5,049,550; Beigelman, *et al.*, US 6,528,640; and Markland, *et al.*, US 5,814,609. The rejection is traversed.

The present invention is directed to a method of preventing or treating diseases or conditions associated with platelet aggregation by administering to a subject a pharmaceutical composition comprising a therapeutic effective amount of **$P2Y_{12}$ receptor antagonist** compound, which is a dinucleotide compound of Formula I, wherein at least one of the Y' and Z' positions is OR_1 or OR_2. The present invention teaches dinucleotide derivatives having at least one modified hydroxyl at 2' or 3' on the sugar moiety for use as inhibitors of $P2Y_{12}$ activation by ADP, thereby inhibiting platelet aggregation.

1. Zamecnik

Zamecnik discloses the use of diadenosine 5',5'''-p^1,p^4-tetraphosphate (AP_4A), or an analogue thereof, as an antithrombotic agent (column 3, lines 4-59). The analogues that Zamecnik refers to only have the modification on the tetraphosphate chain such as CHF, CHCl, and CHBr. Zamecnik does not teach or suggest modification on the ribose moiety. As the Examiner admits, Zamecnik differs from the instantly claimed invention in that (a) Zamecnik does not teach analogs wherein at least one of the 2'- or 3'-positions is OR_1 or OR_2, and (b) Zamecnik does not teach the dinucleotides as $P2Y_{12}$ receptor antagonists.

2. Beigelman, *et al.*

Biegelman, *et al.* disclose examples in the art that describe sugar modifications. Biegelman, *et al.* disclose that oligonucleotides are modified to enhance stability and/or enhance

biological activity by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-O-methly, and 2'-H, nucleotide base modifications (column 16, lines 51-58, column 17, line 41 to column 18, line 6).

(a) Biegelman, *et al.* do not disclose modification of dinucleotides.

Biegelman, *et al.* discloses modification of mononucleotide triphosphates and oligoribonucleotides. Biegelman, *et al.* do not disclose modification of dinucleotides. In oligoribonucleotides, the mononucleotide units are covalently linked through phosphodiester bridges between the 3'-position of ribose of one mononucleotide unit and the 5'-position of ribose of the next mononucleotide unit. Oligonucleotides are different from dinucleotides of the present invention. Dinucleotides are linked through phosphodiester bridges between the 5'-position of sugar of both mononucleotides. Biegelman, *et al.* do not teach or suggest the modification of dinucleotides, nor is there any motivation in Biegelman for modification of dinucleotides.

(b) Biegelman, *et al.* do not disclose a biological activity of treating platelet aggregation.

Beigelman, *et al.* disclose that modifying 2'-OH of oligonucleotides increases the resistance of the oligonucleotides against nuclease. Biegelman's synthetic ribonucleic acids (RNAs) have enzymatic activity; which inhibit HER2/new/ErbB2 gene expression (see Abstract). On the contrary, Applicants' dinucleotides do not have enzymatic activity. Applicants' dinucleotides inhibit ADP-induced platelet aggregation by binding to $P2Y_{12}$ receptors on platelets. There is no hint in Biegelman that by modification of oligonucleotides, the binding to $P2Y_{12}$ receptors will be increased, or the platelet aggregation inhibitory activity will be increased. In the instant application, the substitutions at the 2' and/or 3' positions provide the anti-platelet activity. The stability of the instant dinucleotides is provided mostly by the dinucleotide linkage, not by the ribose substitution. The important features of the present invention are not taught or suggested by Biegelman, *et al.*

(c) Biegelman, *et al.* do not disclose modification of both 2' and 3' hydroxyls (Claims 23-25)

Biegelman, *et al.* only disclose the modification of 2'-OH of ribose. In ribonucleic acids,

the 3'-positions are not free thus they cannot be modified. Biegelman, *et al.* do not teach the modification of both 2'-OH and 3'-OH, therefore, do not teach or suggest the instant Claims 23-25, in which both 2'-OH and 3-OH' are modified.

3. U.S. Patent 5,814,609 (Markland, *et al.*)

Markland, *et al.* discloses that peptides such as contortrostatin found in snake venom can inhibit ADP-induced platelet aggregation. Markland, *et al.* do not disclose purinergic receptors or dinucleotide compounds. The mechanism of action suggested in Markland does not relate to $P2Y_{12}$ receptors; Markland suggests that it relates to binding of the material to GPIIb/IIIa integrin receptors.

4. Combination of References

None of the above-cited references have taught or suggested antagonists of $P2Y_{12}$ purinergic receptors. None of the above-cited references have taught or suggested a dinucleotide compound of Formula I, wherein at least one of the Y' and Z' positions is OR_1 or OR_2. Applicants were the first to make such compounds and to suggest the use of such compounds in preventing or treating platelet aggregation.

Applicants respectfully disagree with the Examiner's assertion that one of ordinary skill would have been motivated to modify 2'-position of AP_4A, based on the teachings of Beigelman, to find more efficacious antithrombotic agents. There is no motivation to combine the two references. First, the chemical structures of the RNA molecules described in Beigelman are very different from that of AP_4A. There is no hint that Beigelman's modification can be applied to AP_4A. Second, Beigelman's modified RNA molecules increase their resistance to nucleases and enhance their enzymatic activities. However, AP_4A is not an enzyme, and one would not extrapolate enhancement of enzymatic activities to enhancement of binding to $P2Y_{12}$ receptors or treating platelet aggregation. Although enzymatic activity and binding activity are both biological activities, they are very different kinds of activities.

Without the teaching of instant application, a skilled person in the art would not have modified dinucleotides on the Y' or Z' position because the outcome is unpredictable and there is no motivation to do so.